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PCRM PHYSICIANS COMMITTEE FOR RESPONSIBLE MEDICINE
5100 WISCONSIN AVENUE, N.W. - SUITE 404
WASHINGTON, DC 20016
T: (202) 686-22 IO - F: (202) 686-2216
PCRM@PCRM.ORG - WWW.PCRM.ORG

October 11, 2000

The Honorable Carol Browner
Administrator
U.S. Environmental Protection Agency
Ariel Rios Building
Room 3000, #1101-A
1200 Pennsylvania Ave., N.W.
Washington, DC 20460

Subject: Comments on "Test Plan for Alkyl Sulfide Category"

Dear Administrator Browner:

The following comments on the Test Plan for Alkyl Sulfide Category are submitted on behalf of the Physicians Committee for Responsible Medicine, People for the Ethical Treatment of Animals, the Humane Society of the United States, the Doris Day Animal League, and Earth Island Institute. These animal protection and environmental organizations have a combined membership of more than nine million Americans concerned with the suffering of animals used in laboratories.

The test plan for alkyl sulfides, submitted by the Chemicals Manufacturers Association (CMA) presents a clear, thorough summary of existing data and test plans. The CMA has judiciously grouped the structurally similar alkyl sulfides into a single category and has demonstrated a thoughtful analysis of existing data to minimize the extent of unnecessary, uninformative tests. The plan presents a category of chemicals that have a consistently low toxicity to all endpoints, including human health. However, due to the physicochemical properties of these compounds, the proposed fish toxicity test and reproductive/developmental toxicity test are not relevant to public health and will not yield a greater understanding of the potential adverse effects of the chemicals.

I can be reached at 202-686-2210, ext. 302, or by e-mail at <ncardello@pcrm.org>. Correspondence should be sent to my attention at the following address: 5 100 Wisconsin Ave., Suite 404, Washington, DC 20016. I look forward to your response on this important issue.

Sincerely,

Nicole Cardello, MHS
Research Coordinator

General Comments on the Test Plan for Alkyl Sulfides

The test plan for alkyl sulfides, submitted by the Chemical Manufacturers Association (CMA) presents a clear, thorough summary of existing data and test plans. The CMA has judiciously grouped the structurally similar alkyl sulfides into a single category and demonstrates a thoughtful analysis of existing data to minimize the extent of unnecessary, uninformative tests. The document clearly describes the course of action and gives extensive justification for development of the category. It is a well thought-out plan that does not approach the testing in a rote checklist manner. However, we have three concerns with the test plan as it is currently presented. They include:

1. The plan could present more of the existing fundamental information on the properties of the compounds in the category, to provide more guidance and insight into the rationale of the test plan.
2. The plan could further discuss the toxicological similarities among all the members in the group in order to further bolster the case for these compounds being included into this logical group.
3. The phy sicochemical properties of these compounds and previous toxicological information preclude the need to conduct the fish toxicity and reproductive/developmental toxicity tests. These tests are not relevant to public health endpoints and will not yield a greater understanding of the potential adverse environmental effects of the chemicals.

Listing of Additional Information

As described in the test plan, the compounds listed in the plan all have high molecular weights (>200 g/mole), are extremely hydrophobic, and all are essentially alkanes and alkenes cross-linked by one or more bridging sulfide or poly sulfide groups, taking roughly the form $R\text{-}S_x\text{-}R'$. The test plan should include more information on the physical and organic chemical behavior of these compounds, including boiling point, melting point, and water solubility. These properties must be understood prior to conducting tests, as they are critical factors to consider in judging whether specific testing is necessary.

Further Documentation and Support for Category Selection

As seen in previous EPA comments, the EPA has been generally reluctant to recognize the appropriateness of categories for human health endpoints.[1] Therefore, in order to prevent unnecessary tests, we would encourage the CMA to further demonstrate the appropriateness and utility of its categories. While the CMA has laid out the general framework for the alkyl sulfide group, we are providing some general comments to strengthen this very appropriate grouping.

- Additional information on sulfide and disulfide metabolism would be useful in developing and understanding this group. In general, organic sulfide compounds tend to exhibit low toxicity. The general lack of toxicity observed in the compounds in this category is consistent with their highly hydrophobic nature, high molecular weights, and the lack of functional groups that are generally associated with more toxic compounds. For example, aromatic, ether, halogen, or furan functional groups tend to be more biochemically reactive than the sulfide and long chain alkenes moieties that are present in these compounds. Overall, a brief review of the structure of all of these compounds would provide more evidence that these compounds present a uniformly low chemical hazard.
- One potential issue relative to the classification of the group is the inclusion of the single propanol derivative (CAS#67124-09-8), as the EPA's guidance for developing structure-activity relation-

ships[2] states that "analogs should have close structural similarity and the same functional groups." However, considering the large size of these molecules and the relatively small effect that a single alcohol group has on the chemical behavior of the compound, the propanol derivative rightly falls into the overall group.

Technical mixtures often contain related compounds that have a variety of functional groups, and may be evaluated with structure activity relationships under HPV guidelines. Just as it is appropriate for these mixtures to be evaluated with SAR relationships, it is also appropriate for an individual compound to be included in a group when it has small variances in chemical structure from other compounds. A single compound should not be excluded from a group due to the presence of a single functional moiety, when it clearly exhibits similar structural, chemical, and toxicological properties as the other category members.

- The weight of evidence presented in the robust summary demonstrates that all category members are essentially non-toxic, associated with few, if any, adverse health effects. The clearest examples of this low toxicity are observed in the acute oral and dermal toxicity tests and the repeat dose toxicity test presented in the robust summaries, where dosing at the EPA-recommended maximum doses leads to minimal toxic effects. The oral LD50s for three of the alkyl sulfide compounds were greater than the limit dose of 5000 mg/kg, while three dermal studies showed the LD50s to be greater than the limit dose of 2000 mg/kg. The fact that these compounds can be applied at these high levels without being acutely toxic is a clear indication that they are minimally toxic.

Despite variations due to high dosing, different exposure routes and vehicles, and interspecies variability, the results are remarkably similar in indicating low toxicity for these compounds. This low toxicity is observed across all the compounds in the group that have been tested. The grouping of these compounds into a single category for analysis of the human health endpoints is therefore appropriate.

Additional Testing Requirements

As shown in the previous discussion, the alkyl sulfides have an overall low toxicity due to their hydrophobic nature, large molecular weight, and lack of toxic functional groups. Given these factors, we believe that the additional acute fish toxicity and reproductive developmental toxicity testing is inappropriate, as described below.

Fish Toxicity

Since the alkyl sulfides are extremely hydrophobic high molecular weight compounds, these chemicals will be found in water at extremely low levels and will have limited ability to be absorbed by fish. Also, due to these physicochemical properties, the alkyl sulfides have limited ability to cross cell membranes and therefore exhibit low biological activity. Since this group of chemicals will not be bioavailable to fish, the fish toxicity testing is unnecessary. The area of fish toxicity is one example where a more complete listing of physical properties in the test plan would be useful. A member of the alkyl sulfide category, methyl propene derivative (CAS # 685 11-50-2), has already been tested for fish acute toxicity in accordance with OECD guideline #203 and did not produce acutely toxic effects.

Reproductive/Developmental Toxicity

As stated above, the alkyl sulfides are hydrophobic, high molecular weight compounds that have difficulty crossing cell membranes. Most of the alkyl sulfides have an average molecular weight exceeding 500, with some molecular weights as high as 2,300. The movement of xenobiotics across the mammalian placenta

occurs primarily by diffusion and is governed, in part, by molecular weight. Xenobiotics with molecular weights greater than 500 will have limited ability to cross the placenta, while those with molecular weights greater than 1000 cannot cross the placenta at all.[3,4] Therefore, transport of the alkyl sulfides across the placenta will be hindered by their high molecular weight. Data on mammalian toxicity through multiple exposure pathways demonstrate the alkyl sulfides to be essentially nontoxic and non-mutagenic. Therefore, it is reasonable to conclude that the alkyl sulfides are not likely to be absorbed by mammals and, if they are absorbed, will have difficulty crossing the placenta and will not produce reproductive or developmental effects.

In short, this test plan makes appropriate use of existing data, but additional consideration needs to be given to further reduce animal testing. We recommend that the fish toxicity and reproductive/developmental tests be omitted.

Conclusions

The weight of the evidence compiled by CMA indicates that the toxicity of the compounds proposed in the alkyl sulfide group is low. Further testing would provide little refinement in the determination of the hazard posed by these compounds, since an abundance of data already exists. This low toxicity is confirmed by the mortality and morbidity of animals used in laboratory experiments and exposed to high doses of alkyl sulfides via multiple routes of exposure. Both professional judgement and common sense call for grouping these highly non-toxic substances into a single category.

References

1. For example, see "EPA Comments on Chemical RTK Challenge Submission: Crude Butadiene C4s"
2. EPA 1999. The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program, found at http://www.epa.ov/opptintr/chemtrk/sarfinl1 .htm.
3. Klaassen, C.D., Amdur, M.O., Doull, J., eds. ***(1986) Casarett and Doull's Toxicology: The Basic Science of Poisons.*** 3rd ed. Macmillan Publishing Company, New York, 212-220.
4. Timbrell, J.A. (199 1) ***Principles of Biochemical Toxicology.*** 2nd ed. Taylor and Francis, London, 241-243.